REMARKS

I. Status of the Claims

Claims 1, 3-6 and 8-13 are pending in the application, and claims 1, 6, 8, 9 and 11-13 stand withdrawn. Thus, claims 3-5 and 10 are under consideration and stand rejected under either 35 U.S.C. §102 or 35 U.S.C. §103. The specific grounds for rejection, and applicant's response thereto, are set out in detail below.

II. Amendments and Alleged Constructive Election

A. Amendments

Claim 4, the only independent claim under consideration, has been amended to employ use of the transitional phrase "consisting of," and thus now recites that Annexin V or a salt thereof, or a dimer and/or a PEG conjugate of Annexin V or salt thereof, is the only active component in the pharmaceutical composition. Also, the claim now defines a particular action for the active component that only Annexin V provides, so that the other active agents are clearly excluded. Finally, the claim now defines the patient group to be treated as a "subject that exhibits vulnerable plaques."

B. Constructive Election

The examiner argues that the alternative claim recitations of Annexin V dimers and PEG conjugates are patentably distinct embodiments, and thus applicant's earlier prosecution of Annexin V is a constructive election allowing these alternative species to be withdrawn.

Without commenting on the patentably distinct nature of these species, applicant traverses the examiner's statement that the species "do not share a common structure that is disclosed to be essential for common utility." Indeed, these species have an ***identical*** common

structure, namely, Annexin V. In one case there are simply two Annexin V molecules, and in the other, the Annexin V is merely PEG-conjugated. Thus, there is unquestionably a common structure. There is no specific assertion by the action, nor any basis to believe, that the mechanism of action (in the context of claim 4) would differ either.

The treatment of Markush-type claims in the context of restriction/election is governed by MPEP §803.02. This section states that "when the Markush group occurs in a claim reciting a process or a combination (not a single compound), it is sufficient if the members of the group are disclosed in the specification ***to possess at least one property in common which is mainly responsible for their function in the claimed relationship, and it is clear from their very nature or from the prior art that all of them possess this property***" (emphasis added). Indeed, it further states that "If the members of the Markush group are sufficiently few in number or so closely related that a search and examination of the entire claim can be made without serious burden, the examiner must examine all the members of the Markush group in the claim on the merits, even though they may be directed to independent and distinct inventions." The examiner is instructed that, in such a case, the provisional election of a single species for prosecution is ***not*** required.

This section further cites to decisions in *In re Weber*, 580 F.2d 455, 198 USPQ 328 (CCPA 1978) and *In re Haas*, 580 F.2d 461, 198 USPQ 334 (CCPA 1978), as support for the rule that it is improper for the Office to refuse to examine that which applicants regard as their invention, unless the subject matter in a claim lacks unity of invention. *In re Harnisch*, 631 F.2d 716, 206 USPQ 300 (CCPA 1980); and *Ex parte Hozumi*, 3 USPQ2d 1059 (Bd. Pat. App. & Int. 1984). More specifically, unity of invention is defined as existing where compounds included within a Markush group (1) share a common utility, and (2) share a substantial structural feature essential to that utility. There simply is no reasonable basis for concluding, in this case, that the

alternative species lack, with the respect to Annexin V, either a common utility or common structural features essential to that utility.

Furthermore, once the examiner determines that Annexin V is allowable, the examination of the Markush-type genus must be extended. Only if prior art is then found that anticipates or renders obvious the Markush-type claim with respect to the rejoinded species will the Markush-type claim be rejected and claims to the nonelected species held withdrawn from further consideration.

In light of these rules, applicant submits that there should be no election under these circumstances, but if there is, rejoinder of the alternative species is required upon the allowability of Annexin V.

III. Rejection Under 35 U.S.C. §102

Claims 4 and 10 are rejected as anticipated by Blankenberg. As explained in detail below, applicants once again traverse.

The examiner has argued that paragraph [0011] of Blankenberg reports that Annexin V itself has anti-apoptotic activity (and other effects, including inhibition of membrane permeability to calcium, protein kinase C and phospholipase A2 *in vitro*). Thus, it is alleged that the reference taught the use of Annexin V alone to prevent plaque rupture. However, this allegation overlooks the following:

(a) Paragraph [0011] of Blankenberg merely discloses that unlabelled Annexin V has anti-apoptotic activity (and other effects, including inhibition of membrane permeability to calcium, protein kinase C and phospholipase A2 *in vitro*). This is not a disclosure of the use of unlabelled Annexin V to prevent plaque rupture.

Blankenberg makes no suggestion that an anti-apoptotic effect (or any of the other effects attributed to Annexin V in Blankenberg) would be useful in the context of preventing plaque rupture.

(b) The other disclosure in Blankenberg regarding using of Annexin V, paragraph [0031], states that "The intrinsic anti-apoptotic properties of internalized annexin V could also be exploited whereby radiolabeled annexin V for imaging could be co-injected with much greater amounts of unlabeled annexin V for therapeutic effect. In addition large saturating quantities of annexin V may also have an *in vivo* anti-inflammatory effect by blocking PS recognition by macrophages and lymphocytes."

Thus, in light of the disclosures that suggest using unlabeled annexin V (a) as a monotherapy for an unspecified "therapeutic effect," and (b) for "*in vivo* anti-inflammatory effect by blocking PS recognition by macrophages and lymphocytes," the examiner argues that putting into effect of either of those teachings by administering unlabelled annexin V to an individual would inherently result in one achieving the technical effect of the present invention.

As discussed above, the claims are now amended, *inter alia*, to further define the subject to be treated one "that exhibits vulnerable plaques." Paragraph [0031] of Blankenberg, which the examiner characterizes as suggesting using Annexin V alone in therapy, does not mention any particular patient population for receiving such a putative monotherapy. Although it is theoretically possible that some unspecified subjects might exhibit atherosclerotic plaques, and further a theoretical possibility that plaques in such individuals could eventually develop into plaques that could rupture, not all subject have plaques, and even fewer have plaques are vulnerable to rupture. Thus, there is no inevitability that treatment of the undefined patient

population from Blankenberg will necessarily include treatment of a patient that possesses rupture-vulnerable plaques. Simply put, paragraph [0031] of Blankenberg does not teach the use of Annexin V alone to treat subjects already having rupture-vulnerable plaques.

The principle of inherent anticipation of method claims is discussed in *King Pharmaceuticals v. Eon Labs v. Elan Pharmaceuticals* (Fed. Cir. 2010; Nos. 2009-1437, 2009-1438), which states that:

> We have held that "[i]t is a general rule that merely discovering and claiming a new benefit of an old process cannot render the process again patentable." *In re Woodruff*, 919 F.2d 1575, 1578 (Fed. Cir. 1990). Such newly discovered benefits are not patentable because they are inherent in the prior art. See *Bristol-Myers Squibb Co. v. Ben Venue Labs., Inc.*, 246 F.3d 1368, 1376 (Fed. Cir. 2001).

Thus, an allegation of anticipation by inherency here would be proper only if the putting into practice of the teaching of para [0031] of Blankenberg inevitably and inherently resulted in the prevention of plaque rupture in individuals that exhibits vulnerable plaques to whom unlabelled annexin V is administered. However, also as stated in *King Pharmaceuticals*:

> ... While inherent anticipation "may not be established by probabilities or possibilities," *In re Oelrich*, 666 F.2d 578, 581 (CCPA 1981), "if the [prior art's] disclosure is sufficient to show that the natural result flowing from the operation as taught would result in the performance of the questioned function, it seems to be well-settled that the disclosure should be regarded as sufficient."

Id. This statement of the law clearly would bar a finding of inherent anticipation where, as here, there is only the mere possibility that a treated patient would have not only atherosclerotic plaques, but those defined by the present claims as being "vulnerable plaques." Thus, given the lack of guidance in paragraph [0031] of Blankenberg for the selection of a patient for treatment, there is ***at best*** only a possibility that the patient treated would have vulnerable plaques. As such, applicant submits that as a matter of law, the disclosure of paragraph [0031] is not sufficient to

show that "the natural result flowing from the operation as taught would result in the performance of" the claimed invention.

A further example of this type of issue being addressed here comes from *Perricone v. Medicis Pharmaceutical* 432 F.3d 1368 (Fed. Cir. 2005), where a prior art disclosure of applying a substance to skin was held not to inherently anticipate a method of treating skin sunburn with that same substance, even though all skin is capable of being sunburned and most if not all skin on all individuals probably possesses some degree of sun damage/sun burn. In finding in favor of the patentee, the court held that:

> The issue is not, as the dissent and the district court imply, whether Pereira's lotion if applied to skin sunburn would inherently treat that damage, but whether Pereira discloses the application of its composition to skin sunburn. It does not .... Claim 1 of the '693 patent recites a new use of the composition disclosed by Pereira, *i.e.*, the treatment of skin sunburn. The district court's inherent anticipation analysis for this claim contains a flaw. The disclosed use of Pereira's lotion, *i.e.*, topical application, does not suggest application of Pereira's lotion to skin sunburn. In other words, the district court's inherency analysis goes astray because it assumes what Pereira neither disclosed nor rendered inherent.

In an analogous fact pattern, the disclosure in paragraph [0031] of Blankenberg for use of unlabelled annexin V in therapy for an unspecified patient group does not amount to a teaching of using unlabelled annexin V in individuals that they would ***necessarily*** have possessed plaques capable of rupture, and thus cannot provide an inherent (*i.e.*, ***inevitable***) disclosure of administering unlabelled annexin V to prevent the rupture of atherosclerotic plaques. Moreover, in light of the present amendments, there is an additional distinction in the present case that may not have been present in the *Perricone* case, namely, that the present claims are amended to specifically restrict the claimed method to a one that is performed on a specific patient group that is not taught or suggested for treatment with unlabelled annexin V by paragraph [0031] of Blankenberg.

The remaining disclosure in Blankenberg fails to teach the use of Annexin V alone. Rather, they describe using a multi-functional molecular probe (see Abstract) comprising Annexin V as a binding component, linked to a cytotoxic moiety (the "effector portion") and a localization moiety (the "targeting portion"). This is clearly not the description of an "active component that binds to and stabilizes the vulnerable plaques consisting of Annexin V or a salt thereof, or consisting of a dimer and/or a PEG conjugate of Annexin V or salt thereof" as required by applicant's amended claim set. As such, these disclosures cannot impact the novelty of claim 4 as presented above.

In sum, the anticipation-by-inherency argument cannot be properly applied to the presently amended claims because the teachings relied upon, *i.e.*, paragraph [0031] of Blankenberg, fail to show that the inevitability of treatment of patients having vulnerable plaques, and further achieving the prevention of plaque rupture in those individuals. Under the controlling law, anticipation will not stand. Reconsideration and withdrawal of the rejection is therefore respectfully requested.

IV. Rejection Under 35 U.S.C. §103

Claims 3-5 are rejected as obvious over Blankenberg in view of Manzi *et al.* Applicants traverse.

Once again, as explained in detail above, Blankenberg does not teach or suggest that Annexin V could be used as a single agent to prevent plaque rupture, and Manzi does not correct this deficiency. Indeed, Manzi says nothing about Annexin V or its uses, and further says nothing about a possible role for apoptosis in plaque rupture. Thus, it too fails to motivate the

skilled person to use Annexin V alone to prevent plaque rupture. Accordingly, even if the skilled person were to have combined Blankenberg and Manzi, their combined teachings still could not render the present invention obvious. Reconsideration and withdrawal of the rejection is therefore respectfully requested.

V. Conclusion

In light of the foregoing, applicants respectfully submit that all claims are in condition for allowance, and an early notification to that effect is earnestly solicited. Should the examiner have any questions regarding this response, a telephone call to the undersigned is invited.

Respectfully submitted,

Steven L. Highlander
Reg. No. 37,642
Attorney for Applicants

FULBRIGHT & JAWORSKI L.L.P.
98 San Jacinto Blvd., Suite 1100
Austin, Texas 78701
(512) 474-5201

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